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Formal Syntheses of Cryptophycin A and Arenastatin A

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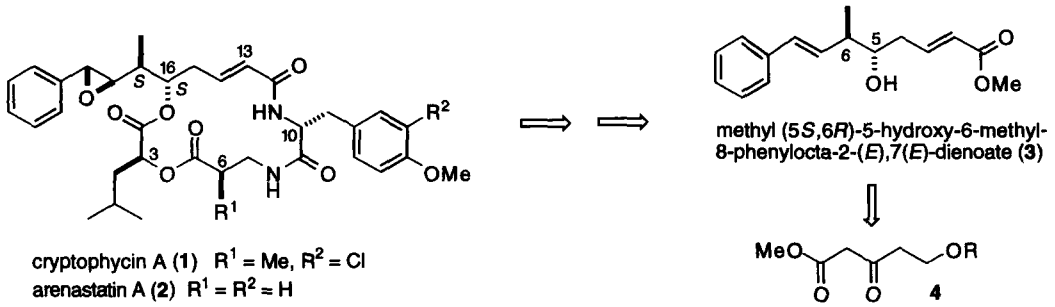
Abstract: Efficient formal syntheses of the tubulin binding antitumor agents cryptophycin A (**1**) and arenastatin A (**2**) are detailed. The readily available β-keto ester **4** was subjected to catalytic asymmetric hydrogenation, Frater alkylation, and selective functional group transformations to provide the silyl ether of octanoic acid methyl ester **3**, which is the key intermediate for the formal syntheses of the title compounds.

The cryptophycins, isolated from blue-green algae (*Nostoc* sp.) by Schwartz *et al.* and Moore and collaborators, are potent fungicides[2] and antitumor agents.[3,4] Among several cryptophycins isolated from the algae, cryptophycin A (**1**, Scheme 1) was the major cytotoxin and displayed IC_{50} values of 3 pg/mL against KB and 5 pg/mL against LoVo cells.[3,4]

Scheme 1



Preclinical *in vivo* investigations with cryptophycin A (i.v.) revealed a remarkable reduction of tumor burden (s.c. transplanted solid tumors of mouse and human origin) and promising gross log tumor cell kill data.[3] Another important property is its reduced susceptibility to P-glycoprotein-mediated multiple drug resistance in comparison to vinblastine, colchicine, and taxol.[5] Semisynthetic modifications of cryptophycin A provided cryptophycin 8, in which the epoxide is converted to a chlorohydrin.[4] This derivative demonstrated better gross log tumor cell kill in comparison to cryptophycin A.[4] Because of the exceptional *in vivo* potency and tumor-selective cytotoxicity of the cryptophycins, clinical trails are planned.[6]

Cryptophycin A is a novel antimitotic agent which induces the depletion of microtubules in A-10 smooth muscle cells and other cells.[5] We[7] and others[8] have recently shown that cryptophycin A binds to the Vinca binding site on tubulin or to a site that overlaps with the Vinca site.

The isolation of a structurally related compound, arenastatin A (**2**), from the Okinawa marine sponge *Dysidea arenaria* was reported recently.[9] The differences in the structures of **1** and **2** are the lack of the chlorine substituent at the C10 benzyl moiety and the C6 methyl group. No detailed biological data have appeared yet for this compound, however, the IC_{50} values for arenastatin A cytotoxicity against KB cells was found to be 5 pg/mL.[9,10]

Although the cryptophycins can be obtained from *Nostoc* cultures, the amounts are relatively small and the separation from the complex algal culture is tideous. Therefore, it is expected that clinically used cryptophycins will be prepared by total synthesis.

Cryptophycin A has been prepared by Barrow *et al.*,[11] Muys and Rej *et al.*,[12,13] and Salamonczyk *et al.*,[14] and two syntheses of arenastatin A have been published by Kobayashi and collaborators.[15,16] Octadienenoic esters of type **3** (Scheme 1) are the key synthetic intermediates for both compounds. Intermediate **3**, which possesses two contiguous chiral centers was prepared employing strategies based on Sharpless methodology,[11,15] on an asymmetric aldol condensation,[16] via a chemoenzymatic approach,[14] and by use of a commercially available chiral starting material, (*S*)-2-acetoxysuccinic anhydride.[12,13]

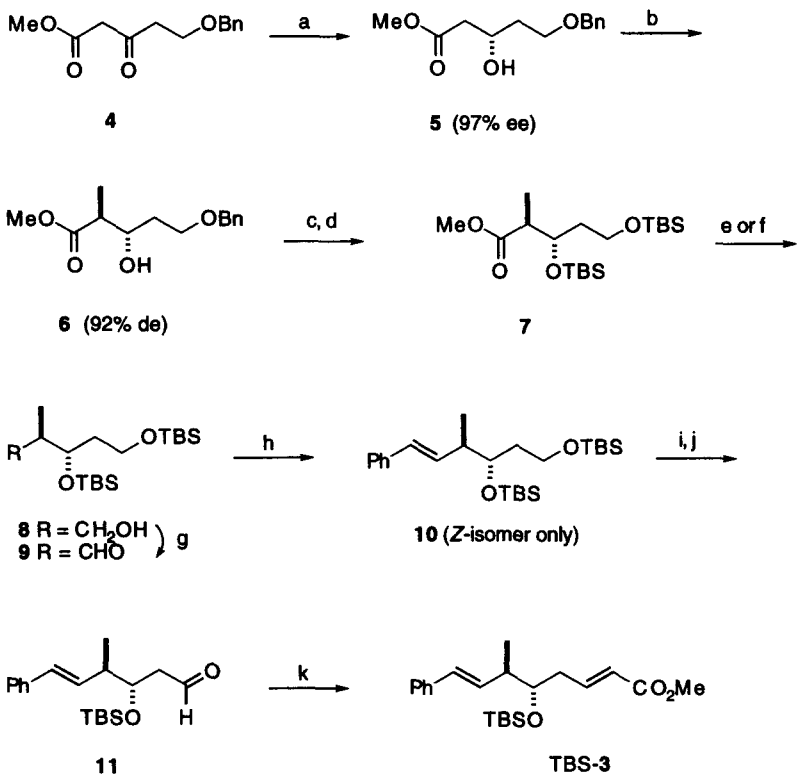
Our continued interest in understanding the interaction of anticancer agents with tubulin,[7] and their structure-activity relationships,[17] prompted us to design an efficient synthesis of building block **3** for the preparation of cryptophycin derivatives and cryptophycin affinity analogues. In this communication we wish to detail a new and efficient route for the synthesis of **3** which can be utilized for the total synthesis as well as for the preparation of analogues of the natural products **1** and **2**. Our retrosynthetic analysis for synthon **3** reveals that it can be obtained from β-keto ester **4** (Scheme 1), which is readily available on a large scale by alkylation of the dianion of methyl acetoacetate[18] with chloromethyl ethers.[18,19] In our approach for the formal synthesis of the target compounds we took the advantage of the well-studied Noyori asymmetric reduction of β-keto esters[20] and combined it with the Frater alkylation[21,22] to introduce the two stereocenters of building block **3**.

As shown in Scheme 2, asymmetric catalytic hydrogenation of **4** with the (*S*)-BINAP-$RuBr_2$ complex[23] under mild conditions (50 °C, 50 psi) provided (*S*)-**5** in 97% yield and 97% ee.[24] Frater alkylation[21,22] of the dianion of β-hydroxyester **5** with methyl iodide gave anti product **6** in 75% yield and 92% diastereomeric excess (de, determined by NMR). The minor isomer was easily removed by flash column chromatography. Debenzylation of **6**, followed by silylation of both hydroxyl groups of the crude intermediate diol, provided bis-silylated **7** in 93% yield. DIBALH reduction of **7** to the corresponding aldehyde (58% yield) and subsequent Horner-Emmons reaction with diethyl benzylphosphonate gave **10** in 74% yield.

The reduction of ester **7** to aldehyde **9** using 1 equiv of DIBALH furnished aldehyde **9** in varying amounts, accompanied by alcohol **8**, depending on solvent and temperature. In one of the experiments (Scheme 2) aldehyde **9** was obtained in 58% and alcohol **8** in 31% yield. Oxidation of alcohol **8** to aldehyde **9** [TPAP (tetrapropylammonium perruthenate),[25] NMO, CH_2Cl_2, 88% yield] provided a combined yield of aldehyde **9** of 85% from ester **7**. In a separate experiment, we converted ester **7** completely to alcohol **8** using 3 equiv of DIBALH (81% yield) and then oxidized (TPAP) alcohol **8** to aldehyde **9** in 88% yield (71% combined yield for the two steps from **7** to **9**). Although, the two step sequence does not provide a higher yield of aldehyde **9**, it is a more convenient procedure than the reduction to the aldehyde since it does not require the chromatographic separation of the alcohol from the aldehyde.

Selective removal of the TBS protecting group at the primary hydroxy group of **10** (HOAc, H_2O, THF; 1:1:2, 82% yield)[26] was followed by TPAP oxidation (78% yield) to give aldehyde **11**, which can be converted to methyl ester TBS-**3** (*E* isomer only) in 83% yield by another Horner-Emmons reaction using TMG (1,1,3,3-tetramethylguanidine) as the base.[11] The final product was compared to the physical and spectral data of TBS-**3** from the literature.[11] A comparison of the optical rotation of our sample of TBS-**3** ($[\alpha]_D$ +67°, *c* 0.63, $CHCl_3$) with the published data for TBS-**3** ($[\alpha]_D$ +68°, *c* 1.5, $CHCl_3$)[11] verified the correct absolute stereochemistry and high optical purity for our product.

Scheme 2



(a) H_2, (*S*)-BINAP-$RuBr_2$, MeOH, 50 °C, 50 psi, 16 h, 97%; (b) LDA, HMPA, MeI, -78 °C, 74%; (c) H_2, Pd/C, THF, 5 h; (d) TBSCl, imidazole, DMF, rt, 12 h, 93%, (2 steps); (e) DIBALH (1.08 equiv), toluene, -60 °C, 1 h, **9** (58%), **8** (31%); (f) DIBALH (3 equiv), THF, -78 °C, 1 h, **9** (81%); (g) TPAP, NMO, CH_2Cl_2:MeCN (10:1), rt, 1 h, 88%; (h) $PhCH_2PO(OEt)_2$, *n*-BuLi, THF, -78 °C to rt, 74%; (i) AcOH:H_2O:THF (1:1:2), rt, 72 h, 82%; (j) TPAP, NMO, CH_2Cl_2, rt, 1 h, 78%; (k) $(MeO)_2POCH_2CO_2Me$, TMG, THF, -78 °C to 25 °C, 83% (ref 10).

In summary, we have detailed a new and efficient route for the synthesis of key intermediate TBS-3 for the synthesis of cryptophycins and arenastatins. The route is suitable for large scale synthesis. Further studies on the preparation of natural products 1 and 2 and related analogues are in progress.

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